Amendments to the Specification:

Please amend the specification as follows:

Please delete paragraph on page 7, line 3 and replace with the following paragraph:

~~As illustrated in Figure 1,~~ mCLK1, mCLK2, mCLK3, and mCLK4 share the essential features identifying them as LAMMER kinases. (Yun et al., Genes. Dev. 8:1160, 1994.) They contain a nuclear localization signal (Dingwall and Laskey, Trends Biochem. Sci. 16:478, 1991), as well as an unusually basic amino terminus composed of many serine and arginine residues. These serine and arginine amino acids likely embody a signal sequence localizing the protein to nuclear speckles. (Hedley et al., PNAS 92:11524, 1995; Colwill et al., EMBO J. 15:265, 1996). The amino terminus is the most divergent portion of the proteins, suggesting that this area could contain information specific to each protein. The catalytic domain is homologous among all family members, with only few amino acid changes. Furthermore, all amino acids known to define the subfamily of CDC2 like kinases are present in all four proteins. (Ben-David et al., EMBO J. 10:317, 1991.)

Please delete paragraph on page 10, line 5 and replace with the following paragraph:

By "isolated" in reference to nucleic acid is meant a polymer of 6 (preferably 21, more preferably 39, most preferably 75) or more nucleotides conjugated to each other, including DNA or RNA that is isolated from a natural source or that is synthesized. In certain embodiments of the invention longer nucleic acids are preferred, for example those of 300, 600, 900 or more nucleotides and/or those having at least 50%, 60%, 75%, 90%, 95% or 99% "identity" to the full length sequence shown in ~~Figure 1, 2, 3, 4 or 5 respectively for PTP20, PCP2, BDP1, mCLK2, mCLK3, mCLK4, or SIRP polypeptide~~ SEQ ID NO: 31 for PTP20, SEQ ID NO: 33 for PCP2 and SEQ ID NO: 35 for BDP1 (Figure 2a-d).

Please delete paragraph on page 12, line 18 and replace with the following paragraph:

The term "PTP20 polypeptide" refers to a polypeptide having an amino acid sequence preferably of at least 400 contiguous amino acids, more preferably of at least 450 contiguous amino acids, or most preferably of at least 453 contiguous amino acids set forth in ~~Figure 1~~ SEQ ID NO: 32, or is substantially similar to such a sequence. A sequence that is substantially similar will preferably have at least 90% identity to the amino acid sequence of ~~Figure 1~~ SEQ ID NO: 32. PTP20 polypeptides preferably have tyrosine phosphatase activity and fragments of the full length PTP20 sequence having such activity may be identified using techniques well known in the art, such as sequence comparisons and assays such as those described in the examples herein.

Please delete paragraph on page 12, line 32 and replace with the following paragraph:

By "a PCP-2 polypeptide" or a "BDP1 polypeptide" is meant 25 (preferably 30, more preferably 35, most preferably 40) or more contiguous amino acids set forth in the full length amino acid sequence of ~~Figure 2 or 3~~ SEQ ID NO: 34 or SEQ ID NO: 36 (Figure 2a-d) respectively, or a functional derivative thereof as described herein. In certain aspects, polypeptides of 100, 200, 300 or more are preferred. The PCP-2 or the BDP1 polypeptide can be encoded by a full-length nucleic acid sequence or any portion of the full-length nucleic acid sequence, so long as a functional activity of the polypeptide is retained.

Please delete paragraph on page 13, line 5 and replace with the following paragraph:

The terms "mCLK2", "mCLK3", and mCLK4" refer to polypeptides that have amino acid sequences substantially similar to those set forth in ~~Figure 4~~ SEQ ID NO: 39, 40 and 41, respectively. A sequence that is substantially similar will preferably have at least 95% identity, more preferably at least 96-97% identity, and most preferably 98-100% identity to the ~~sequence~~ sequences of ~~Figure 4~~ SEQ ID NOS: 5, 39, 40 and 41. CLK protein kinase polypeptides preferably have protein kinase activity and fragments of the full length CLK protein kinase sequences having such activity may be identified using techniques well known in the art, such as sequence comparisons and assays such as those described in the examples herein.

Please delete paragraph on page 12, line 17 and replace with the following paragraph:

By "SIRP polypeptide" is meant 9 or more contiguous amino acids set forth in the full length amino acid ~~sequence~~ sequences of ~~Figure 5~~ SEQ ID NO: 37 (SIRP4) and SEQ ID NO: 38 (SIRP1). The SIRP polypeptides can be encoded by full-length nucleic acid sequences or any portion of a full-length nucleic acid sequence, so long as a functional activity of the polypeptide is retained. Preferred functional activities include the ability to bind to a receptor tyrosine kinase or a SH-2 domain bearing protein such as SHP-2, SHP-1 or Grb-2. A non full-length SIRP polypeptide may be used to elicit an antibody against the polypeptide and the full-length polypeptide using techniques known to those skilled in the art. The present invention also encompasses deltion mutants lacking one or more isolated SIRP domains (e.g., Ig-like domain, transmembrane domain, SH2 binding domain, and tyrosine resideues), and complementary sequences capable of hybridizing to full length SIRP protein under stringent hybridization conditions.

Please delete paragraph on page 13, line 35 and replace with the following paragraph:

A preferred embodiment concerns an isolated nucleic acid molecule relating to PTP20 that encodes at least twelve contiguous amino acids of the amino acid sequence set forth in ~~Figure 1~~ SEQ ID NO: 32. Preferably at least 12, 15, 20, 25, 30, 35, 40, 50, 100, 200 or 300 contiguous amino acids or the PTP20 sequence are encoded. In another preferred embodiment the isolated nucleic acid comprises, consists essentially of, or consists of a nucleic acid sequence, which encodes a PCP-2 or BDP1 polypeptide, set forth in the full length amino acid sequence of ~~Figure 2 or 3~~ SEQ ID NO: 34 or SEQ ID NO: 36, respectively, a functional derivative thereof, or encodes at least 25, 30, 35, 40, 50, 100, 200, 300, 400, 450, 475, or 485 contiguous amino acids are encoded. In another preferred embodiments, isolated nucleic acid comprises, consists essentially of, or consists of a nucleic acid sequence, which encodes a SIRP polypeptide, set forth in the full length amino acid ~~sequence~~ sequences of SEQ ID NOS 37 and 38, or a functional derivative thereof, or at least 25, 30, 35, 40, 5, 100, 200 or 300 contiguous amino acids thereof. These preferred embodiments of the invention are achieved by applying routine recombinant DNA techniques known to those skilled in the art.

Please delete paragraph on page 15, line 5 and replace with the following paragraph:

The nucleic acid may be isolated from a natural source by cDNA cloning or subtractive hybridization; the natural source may be mammalian (human) blood, semen, or tissue of various organisms including eukaryotes, mammals, birds, fish, plants, gorillas, rhesus monkeys, chimpanzees and humans. The nucleic acid may be synthesized by the trimester method or by using an automated DNA synthesizer. In other preferred embodiments the isolated nucleic acid may be at least 95% identical to the nucleic acid sequence shown in ~~Figure 1, 2, 3, 4, or 5~~ SEQ ID NOS: 31, 33 or 35 and is capable of hybridizing to the nucleic acid sequence shown in ~~Figure 1, 2, 3, 4, or 5~~ SEQ ID NOS: 31, 33 or 35, preferably under stringent hybridization conditions.

Please delete paragraph on page 17, line 6 and replace with the following paragraph:

The term "nucleic acid probe" refers to a nucleic acid molecule that is complementary to and can bind a nucleic acid sequence encoding an amino acid sequence substantially similar to that set forth in ~~Figure 1, 2, 3, 4, or 5~~ SEQ ID NOS: 32, 34, 36, 5, 39, 40, 41, 37 or 38.

Please delete paragraph on page 17, line 11 and replace with the following paragraph:

Thus, the nucleic acid probe contains nucleic acid that will hybridize to a sequence set forth in ~~Figure 1, 2, 3, 4, or 5~~ SEQ ID NOS: 31, 33 or 35, or a functional derivative thereof.

Please delete paragraph on page 17, line 14 and replace with the following paragraph:

In preferred embodiments the nucleic acid probe hybridizes to nucleic acid encoding at least 12, 75, 90, 105, 120, 150, 200, 250, 300 or 350 contiguous amino acids of the full-length sequence set forth in ~~Figures 1-3~~ SEQ ID NOS: 32, 34 and 36, at least 17, 20, 25, 30, 35, 40, 50, 100, 200, 300, 400, 450, 475, or 485 contiguous amino acids of the full-length sequence set forth in ~~Figure 4~~ SEQ ID NOS: 5, 39, 40 and 41, or at least 12, 27, 30, 35, 40, 50, 100, 200, or 300 contiguous amino acids of the full-length sequence set forth in ~~Figure 5~~ SEQ ID NOS: 37 and 38, or a functional derivative thereof. Various low or high stringency hybridization conditions may be used depending upon the specificity and selectivity desired.

Please delete paragraph on page 19, line 35 and replace with the following paragraph:

The invention also features recombinant nucleic acid, preferably in a cell or an organism. The recombinant nucleic acid may contain a sequence set forth in ~~Figures 1-5~~ SEQ ID NOS: 31, 33 and 35, or a functional derivative thereof and a vector or a promoter effective to initiate transcription in a host cell. The recombinant nucleic acid can alternatively contain a transcriptional initiation region functional in a cell, a sequence complimentary to an RNA sequence encoding a PTP20, PCP-2, BDP1, mCLK2, mCLK3, mCLK4, or SIRP polypeptide and a transcriptional termination region functional in a cell. The term "recombinant" refers to an organism that has a new combination of genes or nucleic acid molecules. A new combination of genes or nucleic acid molecules can be introduced to an organism using a wide array of nucleic acid manipulation techniques available to those skilled in the art.

Please delete paragraph on page 21, line 26 and replace with the following paragraph:

By "isolated" in reference to a polypeptide is meant a polymer of 2 (preferably 7, more preferably 13, most preferably 25) or more amino acids conjugated to each other, including polypeptides are preferred, such as those with 402, 407, 413, or 425 contiguous amino aicds of PCP-2 set forth in ~~Figure 2~~ SEQ ID NO: 34, those with 400, 450, 475, or 485 of the contiguous amino acids of mCLK2, mCLK3, or mCLK4 set forth in ~~Figure 4~~ SEQ ID NOS: 39, 40 and 41. The isolated polypeptides of the present invention are unique in the sense that they are not found in a pure or separated state in nature. Use of the term "isolated" indicates that a naturally occurring to the natural level this level should be at least 2-5 fold greater, e.g., in terms of mg/ml). Purification of at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated. The substance is preferably free of contamination at a functionally significant level, for example 90%, 95%, or 99% pure.

Please delete paragraph on page 23, line 8 and replace with the following paragraph:

In preferred embodiments, the PTP20 polypeptide contains at least 12, 15, 20, 25, 30, 35, 40, 50, 100, 150, 200, 250, 300, or 350 contiguous amino acids of the full-length amino acid sequence of PTP20 set forth in ~~Figure 1~~ SEQ ID NO: 32, the PCP-2 or BDP1

polypeptide contains at least 25, 30, 35, 40, 50, 100, 150, 200, 250, 300, or 350 contiguous amino acids of full-length sequence set forth in ~~Figures 2 and 3~~ SEQ ID NOS: 34 and 36, respectively, the mCLK2, mCLK3, or mCLK4 polypeptide contains at least 17, 20, 25, 30, 35, 40, 50, 100, 200, 300, 400, 450, 475, or 485 contiguous amino acids of a mCLK2, mCLK3, or mCLK4 polypeptide set forth in ~~Figure 4~~ SEQ ID NOS: 5, 39, 40 and 41, or the SIRP polypeptide contains at least 9, 10, 15, 20, or 30 contiguous amino acids of the full-length ~~sequence~~ sequences set forth in ~~Figure 5~~ SEQ ID NOS: 37 and 38, or a functional derivative thereof.

Please delete paragraph on page 23, line 25 and replace with the following paragraph:

In another aspect, the invention describes a recombinant polypeptide comprising a PTP20, PCP-2, BDP1, mCLK2, mCLK3, mCLK4, or SIRP polypeptide or a unique fragment thereof. By "unique fragment," is meant an amino acid sequence present in a full-length PTP20, PCP-2, BDP1, or SIRP, or minimum stretch of amino acids in one mCLK molecule that is different in sequence than any other portion of another protein kinase or polypeptide that is not present in any other naturally occurring polypeptide. Preferably, such a sequence comprises 6 contiguous amino acids, more preferably 12 contiguous amino acids, even more preferably 18 contiguous amino acids present in the full sequence. For example, since the largest identical stretch of amino acids found among mCLK1, mCLK2, mCLK3 and mCLK4 ~~in Figure 4~~ is seventeen amino acids, the minimum unique fragment for a mCLK protein kinase is seventeen amino acids.

Please delete paragraph on page 26, line 13 and replace with the following paragraph:

In another aspect, the invention provides a nucleic acid molecule comprising a nucleotide sequence that encodes a polypeptide having the full length amino acid sequence set forth in ~~Figure 1, 2, 3, 4, or 5~~ SEQ ID NOS: 32, 34, 36, 5, 39, 40, 41, 37 and 38 except that it lacks at least one domain selected from the group consisting of the N-terminal, catalytic, or C terminal domains. Such deletion mutants are useful in the design of assys for protein inhibitors. The nucleic acid molecules described above may be, for example, cDNA or genomic DNA and may be placed in a recombinant vector or expression vector. In such a

vector, the nucleic acid preferably is operatively associated with the regulatory nucleotide sequence containing transcriptional and translational regulatory information that controls expression of the nucleotide sequence in a host cell.

Please delete paragraph on page 41, line 29 and replace with the following paragraph:

Figure 1 shows ~~the PTP20 nucleic acid sequence isolated from Rat-1 cells and the corresponding amino acid sequence encoded by this nucleic acid molecule~~ a schematic diagram of Figures 2a-d. Figure 2a should be viewed adjacent to figure 2b and figure 2c should be viewed adjacent to figure 2d.

Please delete paragraph on page 41, line 32 in its entirety.

Please delete paragraph on page 42, line 6 and replace with the following paragraph:

FIG. ~~3~~ 2a-d ~~shows~~ show the nucleotide sequence of human BDP1 cDNA clone and introns (SEQ ID NO: 35). The amino acid sequence of human BDP1 is also shown (SEQ ID NO: 36). The sequence first identified by PCR cloning is bordered by arrow heads. A GC-rich track which is part of the Kozak sequence (Kozak, 1987) is indicated by a dotted line. T-rich and the AATAAA sequences required for polyadnylation are underlined. As diagrammed in figure 1, figure 2a should be viewed adjacent to figure 2b and figure 2c should be viewed adjacent to figure 2d.

Please delete paragraph on page 42, line 12 in its entirety.

Please delete paragraph on page 42, line 23 in its entirety.

Please delete paragraph on page 43, line 6 and replace with the following paragraph:

Included within the scope of this invention are the functional equivalents of the herein-described isolated nucleic acid molecules. The degeneracy of the genetic code permits substitution of certain codons by other codons which specify the same amino acid and hence would give rise to the same protein. The nucleic acid sequence can vary substantially since, with the exception of methionine and tryptophan, the known amino acids can be coded for by

more than one codon. Thus, portions or all of the PTP20, PCP-2, BDP1, mCLK2, mCLK3, mCLK4, or SIRP gene could be synthesized to give a nucleic acid sequence significantly different from that shown in ~~Figures 1-5~~ SEQ ID NOS: 31, 33 and 35. The encoded amino acid sequence thereof would, however, be preserved.

Please delete paragraph on page 43, line 20 and replace with the following paragraph:

In addition, the nucleic acid sequence may comprise a nucleotide sequence which results from the addition, deletion or substitution of at least one nucleotide to the 5'-end and/or the 3'-end of the nucleic acid ~~formula~~ sequence shown in ~~Figures 1-5~~ SEQ ID NOS: 31, 33 and 35 or a derivative thereof. Any nucleotide or polynucleotide may be used in this regard, provided that its addition, deletion or substitution does not alter the amino acid sequence of ~~Figures 1-5~~ SEQ ID NOS: 32, 34 and 36 which is encoded by the nucleotide sequence. For example, the present invention is intended to include any nucleic acid sequence resulting from the addition of ATG as an initiation codon at the 5'-end of the inventive nucleic acid sequence or its derivative, or from the addition of TTA, TAG or TGA as a termination codon at the 3'-end of the inventive nucleotide sequence or its derivative. Moreover, the nucleic acid molecule of the present invention may, as necessary, have restriction endonuclease recognition sites added to its 5'-end and/or 3'-end.

Please delete paragraph on page 56, line 28 and replace with the following paragraph:

The present invention relates to an antibody having binding affinity to a PTP20, PCP-2, BDP1, mCLK2, mCLK3, mCLK4, or SIRP polypeptide. The polypeptide may have the amino acid sequence set forth in ~~Figures 1-5~~ SEQ ID NOS: 32, 34, 36, 5, 39, 40, 41, 37 and 38, or functional derivative thereof, or at least 9 contiguous amino acids thereof (preferably, at least 20, 30, 35, or 40 contiguous amino acids thereof).

Please add the following new paragraph at page 69, line 31:

PTP20 nucleic acid was isolated from Rat-1 cells (SEQ ID NO: 31). The corresponding amino acid sequence encoded by this nucleic acid molecule was determined (SEQ ID NO: 32).

Please add the following new paragraph at page 69, line 31 after the above paragraph:

The PCP-2 nucleotide sequence (5581 bp) (SEQ ID NO: 33) and deduced amino acid sequence (1430 amino acid) (SEQ ID NO: 43) were determined. The predicted initiating methionine (Kozak, 1984), putative signal peptide (von Heijne, 1986), transmembrane domain, two tandem phosphatase domains, MAM domain, Ig-like domain and four fibronectin type III-like domains were identified. The polyadenylation motif (AATAAA) was also identified.

Please add the following new paragraph at page 69, line 31 after the above paragraph:

The nucleotide sequence of human BDP1 cDNA (SEQ ID NO: 35) and amino acid sequence of human BDP1 (SEQ ID NO: 36) were determined. In figure 2a-d the sequence first identified by PCR cloning is bordered by arrow heads. A GC-rich track which is part of the Kozak sequence (Kozak, 1987) is indicated by a dotted line. T-rich and the AATAAA sequences required for polyadnylation are underlined.

Please add the following new paragraph at page 69, line 31 after the above paragraph:

The amino acid sequences (SEQ ID NOS 5, 39, 40 & 41 respectively) encoded by mCLK1, mCLK2, mCLK3, and mCLK4 nucleic acid molecules cloned from mouse cells were compared. Each amino acid sequence is encoded between a start codon and a stop codon from its respective nucleic acid molecule. The predicted nuclear localization signals, amino acids signifying CDC2 like kinases, catalytic domain, and LAMMER signature were identified.

Please add the following new paragraph at page 69, line 31 after the above paragraph:

The deduced amino acid sequences of SIRP4 and SIRP1 (SEQ ID NOS 37 & 38 respectively) were determined and compared. The putative signal sequence, ~~and~~ transmembrane region, three Ig-like domains, potential tyrosine phosphorylation sites C-terminal proline rich region, and oligonucleotides flanking the Ex region were identified.

Please delete paragraph on page 70, line 18 and replace with the following paragraph:

The degenerate primers used to identify PTP20 were FWXMXW (SEQ ID NO: 1) (sense) and HCSAG(S/I/V)G (SEQ ID NO: 2) (antisense). Random-primed cDNA (up to 50 ng) from PC12 cell RNA was used as a template. Both sense and antisense primers were added to a 100 ml reaction mixture containing 20 mM Tris-HCl (pH 8.4), 50 mM-KCl, 2.5 mM MgCl2, 0.01% BSA, all four dNTPs (each at 200 mM), 1 unit of Taq polymerase (Boehringer Mannheim) and template cDNA. Thirty-five cycles were carried out on a thermal cycler; each cycle involved incubation at 94°C for 1 min, at 42°C for 1 min and 72°C for 1 min. The PCR products were separated on a 1.5% agarose gel. Fragments of 350-400 bp were excised, subcloned and sequenced.

Please delete paragraph on page 71, line 15 and replace with the following paragraph:

We used sequence homology and PCR amplification to clone the protein tyrosine phosphatases expressed in human brain tissue. The degenerate primers for PCR were designed according to the consensus sequences from alignment of amino acid sequences of known PTPases. The longest consensus sequences FWXMXW (SEQ ID NO: 1) and HCSAGXG (SEQ ID NO: 2) in catalytic domains were selected. A single-lane sequencing of 379 amplified CDNA clones identified 15 different CDNA clones, including CD45, LAR, MEG1, PTPase, PTPase, PTPase, PTPase, PTPase, PTPase and PTPase 1D. One clone encoded a novel putative protein tyrosine phosphatase. We called the clone BDP1 because it was found in human brain cDNA.

Please delete paragraph on page 71, line 28 and replace with the following paragraph:

The CR-amplified BDP1 clone was used for screening cDNA libraries. Screened first were the cDNA libraries related to human brain tissue, such as fetal brain, amygdale and pituitary. Comparison of the nucleotide sequence of the BDP1 PCR product and 1.1 Kb BDP1 from human fetal brain cDNA library revealed introns in the fetal brain clone. More than half of 23 positive clones were found to be imperfectly spliced. As is already known, these intron sequences start as GT and end as AG. We tried specific PCR primers, designed on the basis of sequence comparison, to differentiate between complete clones and

incomplete ones with intron sequences. Three introns of 367, 80 and 91 bp-long sequences were found at the position of the nucleotide 733, 799 and 878~~, respectively (Fig. 1B). The locations of introns are indicated by arrow heads in Fig. 1A~~.

Please delete paragraph on page 72, line 17 and replace with the following paragraph:

The degenerate primers used to identify BDP1 were FWXMXW (SEQ ID NO: 1) (sense) and HCSAG(S/I/V)G (SEQ ID NO: 2) (antisense). 2 μg of human brain poly(A)+RNA were used for the synthesis of the first-strand cDNA, employing oligo(dT)-priming and RNase H-negative reverse transcriptase (GIBCO/BRL). 50 ng of synthesized cDNA were amplified with 30 pmol of each degenerate primer in 100 μl of PCR solution for 30 cycles. Amplified PCR-products were digested with BamHI or EcoRI and separated on 6% acrylamide gel. Fragments of about 350 bp were excised, subcloned and sequenced.

Please delete paragraph on page 73, line 4 and replace with the following paragraph:

The longest clone from the MEGO1 cDNA library was 2810 bp long and contained a single long open reading frame (ORF) of 1377 bp which was preceded by a 5'-noncoding region without a stop codon. Its overall G+C content was 57%. There were no long ORF in the 3'-noncoding sequence. This clone had no intron sequences that were detected in other clones. Only both 5'- and 3'-flanking primer regions were slightly different, but the 340 bp sequence between primers perfectly matched the BDP1 pCR product ~~(see box in Fig. 1A)~~.

Please delete paragraph on page 73, line 14 and replace with the following paragraph:

The ATG at the beginning of the ORF was flanked by a sequence that conforms to the Kozak consensus for translation initiation like the GB-rich track (Kozak, M. (1987). Nucleic Acids Res. 15, 8125-8248). Purine base was identified in position -3 and A instead of G in position +4. The 3'-noncoding region contains two distinct sequence elements which are required for accurate and efficient polyadenylation (15). One element T-rich sequence was located 200 nucleotides downstream and another AATAAAA was 20 nucleotides downstream from the poly(A)- tail. ~~The two elements are underlined in Fig. 1A.~~

Please delete paragraph on page 73, line 26 and replace with the following paragraph:

The ORF of BDP1 is a residue with 459 amino acids, and it encodes a protein of approximately 50 KDa. The putative catalytic region of predicted protein sequence – amino acids 59 to 294 – contains all of the highly conserved sequence motifs found in most protein tyrosine phosphatases, including a Cys and ARG in the phosphate-binding loop, with thse being essential for PTPase catalytic activity (Barford, D., Flint, A.J. and Tonks, N.K. (1994) Science 263, 1397-1404; Stuckey et al. (1994). Nature 370, 571-575; Su, et al. (1994) Nature 370, 575-578; Zhang, et al. (1994) Proc. Natl. Acad. Sci. USA 91, 1624-1627). ~~The highly conserved amino acid residues are shown in the boxes in Fig. 2A.~~

Please delete paragraph on page 74, line 12 and replace with the following paragraph:

The deduced amino acid sequence from aa 1 to 25 at the N-terminus was compared with sequences in data banks. It was found that the 70 KDa cyclase-associated CAP protein of yeast (Field, et al. (1990) Cell 61, 319-327), rat (Selicof, et al. (1993) J. Biol. Chem. 268, 13448-13453) and human (Matviw, et al (1992) Mol. Cell. Biol. 12, 5033-5040) were homologous, as is illustrated in FIG. 2B. Especially the FLERLE (SEQ ID NO:3) sequence could also be found in the acidic FGF molecule near the second Cys consensus residue, and was also reported to take part in the binding to its own receptor molecule on the cell surface (Thomas, et al. (1991). Ann. New York. Acad. Sci. 9-17).

Please delete paragraph on page 74, line 34 and replace with the following paragraph:

The 160 aa-long-tail sequence from the 295th amino acid residue has no homology with known proteins, nor do PEST motifs (Rogers, et al. (1986). Science 243, 364-368). The PTPase-PEST family has a long tail containing the nuclear localization signal in PEP (Flores, et al. E., Roy, G., Patel, D., Shaw, A. and Thomas, M.L. (1994) Mol. Cell. Biol. 14, 4938-4946) and the serine phosphorylation site in human PTPas-PEST (Farton, A.J. and Tonks, N.K. (1994) PTP-PEST: a protein tyrosine phosphatase regulated by serine phosphorylation. EMBO J. 13, 3763-3771). All these sequences are not contained in BDP1 at the tail sequence were 11.4, 4.8, 6.0 and 6.6%, respectively. The E, S and T contents were much lower, but P was higher than the PTPase- PEST-family phosphatases. The molecular weight of BDP1, namely 50 KDa, was much lower than that of PTPase-PEST (88 KDa) and that of

hematopoietic PTPase-PEST (90 KDa). The short half-life of PTPase in cells, due to the PEST motif, must still be investigated. However, the BDP1 sequence of the last 22 amino acids at the carboxy terminus were similar to two PTPases with PEST motif~~, as shown in Fig. 2C~~.

Please delete paragraph on page 76, line 9 and replace with the following paragraph:

PCR reactions were performed using degenerate oligonucleotide primers corresponding to the consensus sequences RWXMXW (SEQ ID NO: 4) and HCSAG (S/I/V) G (SEQ ID NO: 2), and the GeneAmp.RTM. kit (Perkin-Elmer/Cetus) and pool of poly (A)+RNA from 9 human pancreatic carcinoma cell lines: A590, A818-7, AsPc 1, BxPC-2, Capan-1, Capan-2, Colo357, DAN-G and SW850 (ATCC, Rockville, Md.). The PCR fragments were isolated, subcloned, and sequenced.

Please delete paragraph on page 80, line 3 and replace with the following paragraph:

The PTP20 mutant containing a cysteine to serine alteration at position 229 was generated using a oligonucleotide primer, CTCTGTGTCCACAGCAGTGCTGGCTGT (SEQ ID NO: 6). Kunkel, PNAS 82:488, 1985.) The mutation was confirmed by DNA sequencing.

Please delete paragraph on page 88, line 6 and replace with the following paragraph:

The signature sequences HRDLAAR (SEQ ID NO: 7) in the catalytic subdomain VI and D(V/M)WS(Y/F)G (SEQ ID NO: 8) in subdomain IX were used to create degenerate oligonucleotides. (Ciossek et al., Oncogene 11:2085, 1995.) Reverse transcriptase PCR reactions were performed with 2 μg of total RNA prepared from confluent or differentiated (day 7) mouse C2C12 myoblasts (Lechner et al., PNAS 93:4355, 1996). (Ciossek et al., Oncogene 11:2085, 1995.) Briefly, 2 μg of RNA were reverse transcribed in the presence of 1 μM degenerate antisense primer, 250 μM of each nucleotide and 75 units of Stratascript reverse transcriptase (Stratagene) in a total volume of 20 μl for 30 min at 42°C 2 μl of the above reaction was used in a PCR reaction using degenerate sense and antisense oligonucleotides (1 μM each), 25 μM of each nucleotide and 2.5 units Taq polymerase

(Boehringer). 30 cycles were performed with 1 min for each 94°C, 50°C and 72°C step. Fragments of approximately 250 bp were gel purified, cloned in Bluescript and sequenced.

Please delete paragraph on page 88, line 24 and replace with the following paragraph:

mCLK2, mCLK3 and mCLK4 were cloned from a mouse embryo 11.5 p.c. 1ZAP cDNA library (Ciossek et al., supra) using the isolated PCR fragment as a probe according to manufacturer's instructions (final wash in 0.5X SSC/0.1% SDS at 42°C) (Stratagene). mCLK1 was cloned by reverse transcriptase PCR from 1 μg brain poly $(A)^+$ RNA using specific primers mCLKls-Bam, CGGGATCCCTTCGCCTTGCAGCTTTGTC (SEQ ID NO: 9) and mCLKlas-EcoRI, CGGAATTCCTAGACTGATACAGTCTGTAAG (SEQ ID NO: 10), and Pwo polymerase (Doehringer).

Please delete paragraph on page 88, line 33 and replace with the following paragraph:

From the approximately 300 fragments which were sequenced from the first PCR reaction, one was novel. It resembled a member of the LAMMER family of dual specificity kinases (Yun et al., Genes. Dev. 8:1160, 1994), also known as CLK kinases (Ben-David et al., EMBO J. 10:317, 1991) or STY (Howell et al., Mol. Cell. Biol. 11:568, 1991) and shared a high homology to a part of the human cDNA hCLK2. Full length clones of this and three related proteins were obtained from a mouse embryonic cDNa library as described. The same libraries were rescreened with a mixture of mCLK1, 2, 3, and 4 fragments at low stringency to isolate additional novel members of this family. Reverse transcriptase PCR reactions were performed on brain, kidney and liver poly $(A)^+$ RNA with degenerate primers coding for the DLKPEN (SEQ ID NO: 11) and AMMERI (SEQ ID NO: 12) motifs. These efforts did not identify additional genes.

Please delete paragraph on page 90, line 30 and replace with the following paragraph:

GST fusion constructs were generated by subcloning full length mCLK1, mCLK2, mCLK3 and mCLK4 cDNAs by PCR into pGEX vectors (Pharmacia), creating in-frame glutathione S-transferase (GST) fusion constructs using the-following primers for PCR: mCLKls-Bam (as above); mCLKlas-Not I,

TATAGCGGCCGCTAGACTGATACAGTCTGT (SEQ ID NO: 13); mCLK2s-Sma I, TCCCCCGGGATGCCCCATCCCCGAAGG- TACCA (SEQ ID NO: 14); mCLK2as-Not I, TATAGCGGCCGCTCACCGACTGATATCCCGACTGGAGTC (SEQ ID NO: 15); mCLK3s-Sma I, TCCCCCGGGGAGACGATGCATCACTGTAAG (SEQ ID NO: 16); mCLK3as-Not I, TATAGCGGCCGCGCTGGCCTGCACCTGTCATCTGCTGGG (SEQ ID NO: 17); mCLK4s-EcoRI, CGGAATTCATGCGGCATTCCAAACGAACTC (SEQ ID NO: 18), mCLK4as-Not I, TATAGCGGCCGCCCTGACTCCCACTCATTTCCTTTTTAA (SEQ ID NO: 19). The cDNAs encoding the fusion construct were then recloned in pcDNA3 (Invitrogen) by PCR using the GST upstream primers: GST-EcoRI, CGGAATTCCGCCACCATGGCCCCTATACTAGGTTAT (SEQ ID NO: 20) (for mCLK1) and GST-Hind III, GCCAAGCTTGCCACCATGGCCCCTATACTA- GGTTAT (SEQ ID NO: 21) (for mCLK2, mCLK3 and mCLK4).

Please delete paragraph on page 91, line 9 and replace with the following paragraph:

Integrity of the clones was checked by sequencing and by a coupled transcription-translation assay using T7 RNA polymerase and rabbit reticulocyte lysate according to the manufacturer's protocol (Promega). mCLK 1-4 mutants containing a lysine (K) to arginine (R) substitution at position 190 (mCLK1), 192 (mCLK2), 186 (mCLK3) and 189 (mCLK4) were generated using a site-directed mutagenesis protocol. (Kunkel, PNAS 82:488-, 1985.) Oligonucleotide primers were as follows: (mCLK1-K190R) GTAGCAGTAAGAATAGTTAAA (SEQ ID NO: 22); (mCLK2-K192R) GTTGCCCTGAGGATCATTAAGAAT (SEQ ID NO: 23); (mCLK3-K186R) GTTGCCCTGAGGATCATCCGGAAT (SEQ ID NO: 24); (mCLK4-K189R) TACAATTCTCACTGCTACATGTAAGCCATC (SEQ ID NO: 25).

Please delete paragraph on page 96, line 27 and replace with the following paragraph:

Insulin treated Rat1-IR were used to purify the 110 kDa SHP-2 binding glycoprotein using standard chromatography procedures. Approximately 4 mg of the glycoprotein that copurified with SHP-2 were obtained and subject to microsequence analysis. This yielded five peptide sequences: PIYSFIGGEHFPR (SEQ ID NO: 26), IVEPDTEIK (SEQ ID NO: 27), YGFSPR (SEQ ID NO: 28), IKEVAHVNLEVR (SEQ ID NO: 29), VAAGDSAT (SEQ

ID NO: 30). Computer aided search in the EST database led to the identification of a 305 bp rat sequence (accession Nr.: H31804) and subsequent human cDNA fragment of 2 kb (EMBL databank, accession Nr.: U6701) containing matching and homologous sequences, respectively.

Please delete paragraph on page 73, line 4 and replace with the following paragraph:

The longest clone from the MEGO1 cDNA library was 2810 bp long and contained a single long open reading frame (ORF) of 1377 bp which was preceded by a 5'-noncoding region without a stop codon. Its overall G+C content was 57%. There were no long ORF in the 3'-noncoding sequence. This clone had no itron sequences that were detected in other clones. Only both 5"- and 3"- flanking primer regions were slightly different, but the 340 bp sequence between primers perfectly matched the BDP1 PCR product ~~(see box in Fig. 1A)~~.

Please delete paragraph on page 73, line 14 and replace with the following paragraph:

The ATG at the beginning of the ORF was flanked by a sequence that conforms to the Kozak consensus for translation initiation like the GC-rich track (Kozak, M. (1987). Nucleic Acids Res. 15, 8125-8248). Purine base was indentified in position -3 and A instead of G in position +4. The 3'-noncoding region contains two distinct sequence elements which are required for accurate and efficient polyadenylation (15). One element T-rich sequence was located 200 nucleotides downstream and another AAATAAAA was 20 nucleotides downstream from the poly(A)+ tail. ~~The two elements are underlined in Fig. 1A.~~

Please delete paragraph on page 73, line 26 and replace with the following paragraph:

The ORF of BDP1 is a residue with 459 amino acids, and it encodes a protein of approximately 50 KDa. The putative catalytic region of predicted protein sequence – amino acids 59 to 294 – contains all of the highly conserved sequence motifs found in most protein tyrosine phosphatases, including Cys and Arg in the phosphate-binding loop, with these being essential for PTPase catalytic activity (Barford, D., Flint, A.J. and Tonks, N.K. (1994) Science 263, 1397-1404; Stuckey, et al. (1994). Nature 370, 571-575; Su, et al. (1994) Nature

370, 575-578; Zhang, et al. (1994) Proc. Natl. Acad. Sci. USA 91, 1624-1627). ~~The highly conserved amino acid residues are shown in the boxes in Fig. 2A.~~

Please delete paragraph on page 74, line 34 and replace with the following paragraph:

The 160 aa-long-tail sequence from the 295th amino acid residue has no homology with known proteins, nor do PEST motifs (Rogers, et al. (1986). Science 234, 364-368). The PTPase-PEST family has a long tail containing the nuclear localization signal in PEP (Flores, et al. E., Roy, G., Patel, D., Shaw, A. and Thomas, M.L. (1994) Mol. Cell. Biol. 14, 4938-4946) and the serine phosphorylation site in human PTPase-PEST (Farton, A.J. and Tonks, N.K. (1994) PTP-PEST: a protein tyrosine phosphatase regulated by serine phosphorylation. EMBO J. 13, 3763-3771). All these sequences are not contained in BDP1 PTPase. The amino acid composition of P, E, S and T of BDP1 at the tail sequence were 11.4, 4.8, 6.0 and 6.6%, respectively. The E, S and T contents were much lower, but P was higher than the PTPase- PEST-family phosphatases. The molecular weight of BDP1, namely 50 KDa, was much lower than that of PTPase-PEST (88 KDa) and that of hematopoietic PTPase-PEST (90KDa). The short half-life of PTPase in cells, due to the PEST motif, must still be investigated. However, the BDP1 sequence of the last 22 amino acids at the carboxy terminus were similar to two PTPases with motif~~, as shown in Fig. 2C~~.

Drawings:

Please substitute the attached 5 sheets (Figs. 1, 2a, 2b, 2c, and 2d) of formal drawings for the informal drawings originally filed with the application. A separate Transmittal of Formal Drawings is submitted.

The drawing sheets attached in connection with the above-identified application containing Figures 1 – 2d are being presented as formal drawing sheets to be substituted for the previously submitted informal drawing sheets. No new matter has been added to the figures.